IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE AG, ALCON, INC. and ALCON MANUFACTURING, LTD. Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	)	Civil Action No. 06-234 (SLR) **PUBLIC REDACTED VERSION**

DEFENDANT TEVA PHARMACEUTICALS USA, INC.'S
OPENING POST-TRIAL BRIEF
ON THE INVALIDITY OF U.S. PATENT NO. 6,716,830

May 22, 2008

BAYARD, P.A.

Richard D. Kirk (#0922)
Ashley B. Stitzer (#3891)
222 Delaware Avenue, Suite 900
P.O. Box 25130
Wilmington, DE 19899-5130
rkirk@bayardfirm.com
astitzer@bayardfirm.com
(302) 655-5000
Counsel for Defendant,
TEVA PHARMACEUTICALS USA, INC.

OF COUNSEL:

Bruce M. Gagala
M. Daniel Hefner
Douglas A. Robinson
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
Chicago, Illinois 60601

TABLE OF AUTHORITIES

Page

Cases

Statutes

Rules

Constitutional Provisions

TABLE OF CONTENTS

SUMMARY OF ARGUMENT

If the Court construes "moxifloxacin" as Teva contends, then Teva does not assert that claim 1 of the '830 patent is invalid in light of the prior art. If, however, the Court resolves claim construction in Alcon's favor, then Teva asserts that claim 1 of the '830 patent is invalid under 35 U.S.C. § 102(b) and § 103(a) as anticipated and obvious, because there is simply no invention here. The inventors merely exchanged moxifloxacin for previously-known antibiotic compounds in prior-art ophthalmic compositions, without any testing of any formulation. The inventors did no more than exercise common sense, with the anticipated success, later confirmed. Indeed, U.S. Patent No. 5,607,942 ("the '942 patent") discloses every element of claim 1 of the '830 patent.

Regardless of how the Court construes claim 1 of the '830 patent, claim 1 is invalid for failure to comply with the best mode, written description, and enablement requirements of 35 U.S.C. § 112, first paragraph. Clear and convincing evidence establishes the following:

- As of their September 1998 priority date, the inventors of the '830 patent knew of only one form of moxifloxacin: BAY 12-8039, which was, by law, their best mode. However, the inventors did not disclose the use of BAY 12-8039 in the description of the '830 patent, thus concealing their best mode of practicing the invention in violation of § 112.
- Claim 1 of the '830 patent does not require a preservative, which the specification states is required. Thus, the scope of the right to exclude claimed by the patentees is broader than the specification of the '830 patent, violating both the written description and enablement requirements of § 112.
- Claim 1 is further not enabled if the Court adopts Alcon's proposed definition of the "person" of ordinary skill in the art (the level of skill in the art, and the definition of a

"person of ordinary skill" is a contested issue of fact in this case). The '830 patent only discloses ingredient lists for a few compositions containing moxifloxacin, but it does not disclose any direction at all, to Alcon's alleged "person" of ordinary skill as to how to make any composition. The person of ordinary skill advocated by Alcon would not have sufficient skill to fill in these gaps in the patent so as to be able to make the many types of compositions throughout the full scope of claim 1 without undue experimentation.

THE TESTIMONY OF DR. MITRA, AN ALCON EXPERT, SHOULD BE EXCLUDED

At trial, counsel for Teva objected to Dr. Mitra's testimony and reliance on certain data relating to ocular penetration of moxifloxacin in an animal study, which was contained in PTXs 364, 365, and 366, and his opinions based thereon, because these data and his related testimony contradicted the opinion expressed in his expert report and prior deposition testimony. The Court directed that this matter be addressed in post-trial briefs. Tr. 814:8–14.

At his deposition on November 6, 2007, Dr. Mitra testified that the *only* moxifloxacin composition for which he had examined ocular penetration data was Vigamox®, a commercial product. Tr. 770:12–771:21. At trial, Dr. Mitra admittedly changed his testimony, stating that the vehicles tested in PTX 1116 were not commercial products but were instead the same for each composition tested. Tr. 807:19–811:3. This was a material change in Dr. Mitra's opinion, as he testified repeatedly that the vehicle can have an effect on ocular penetration. Tr. 761:10–16, 782:5–783:9, 823:19–25.

Dr. Mitra tried to excuse his change-in-opinion at trial by stating that during his prior deposition testimony regarding what became PTX 1116, that he had simply been "guessing" that the compositions used in those tests were commercial products containing different vehicles (i.e.,

different excipients[1]), and that he thereafter "wanted the lab notebooks" so he could find the data allegedly supporting that exhibit. Tr. 762:4–18. Dr. Mitra also testified that his new opinion was based on the data he had since been given access to. Tr. 743:12–22.

At trial, counsel for Alcon represented that certain notebooks somehow relevant to Dr. Mitra's testimony had been produced to Teva during discovery. Tr. 810:18–814:7. However, the notebooks were produced to Teva only *after* Dr. Mitra's deposition (Tr. 813:12–21), even though the notebooks plainly existed and were in Alcon's possession well before Dr. Mitra prepared his expert report and well before his deposition, as the notebooks are dated November 2003, January 2004, and May 2007, respectively. See PTXs 364, 365, 366. Furthermore, while Alcon sent Teva a volume of technical information after Dr. Mitra's deposition, Alcon did nothing more. Importantly, Alcon offered no explanation of the notebooks' pertinence to Dr. Mitra's opinion (or the changes in his opinion) by way of a supplemental report or otherwise.

Under these circumstances, Fed. R. Civ. P. 26(e) placed an affirmative burden on Alcon to have provided a supplemental expert report so that Teva would have notice not only that additional information was considered, but also how Dr. Mitra's opinion had changed as a result. "Supplementation under the Rules means correcting inaccuracies, or filling the interstices of an incomplete report based on information that was not available at the time of the initial disclosure." *Keener v. U.S.*, 181 F.R.D. 639, 640 (D. Mont. 1998). Alcon failed to comply with Rule 26, and this failure prejudiced Teva in preparing for trial. Accordingly, the Court should strike PTX 364, 365, 366, and 1116 and Dr. Mitra's testimony related thereto.

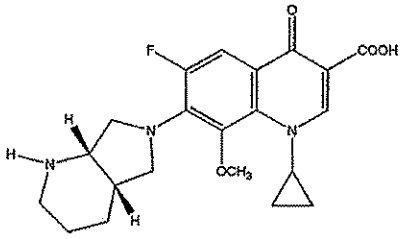
[1] "Excipients" are the ingredients in a formulation that are used to make the formulation pharmaceutically acceptable. (Tr. 192:19–193:5).

While Alcon may argue that Teva could have sought to re-depose Dr. Mitra, in the absence of a supplemental expert report from Alcon, Teva had no reason to question that Dr. Mitra's opinion had changed, and therefore no reason to expend further resources deposing him again. More pertinently, the affirmative burden was simply not on Teva to seek to ascertain how or why Dr. Mitra's opinions may have changed after his deposition. Rather than follow Rule 26, Alcon chose to "not meet its disclosure obligations by telling [Teva], in effect, that [Teva] can unearth the basis of the expert's opinions by plowing through [a volume of] of data without further guidance." *Williams v. Roberts*, 202 F.R.D. 294, 296 (M.D. Ala. 2001); *see also Erickson v. Baxter Healthcare, Inc.*, 131 F. Supp. 2d 995, 1000–1001 (N.D. Ill. 2001) (reference to series of articles without identifying specific pages supporting the opinion was unacceptable, and akin to "bringing a motion and offering as support only a reference to the 'United States Code.'"). Dr. Mitra's trial testimony as to unexpected results, based as it was on the improperly disclosed data, should thus be excluded under Fed. R. Civ. P. 37(c)(1).

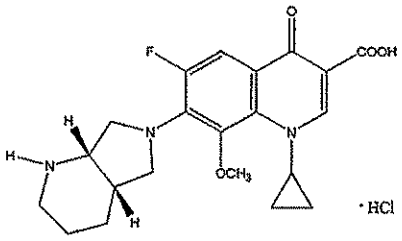
Independently, Dr. Mitra's opinions should also be excluded under Fed. R. Evid. 702, as his own testimony shows him to be unreliable. Compounding his admission that he had formulated his opinions for this action based on data unseen by him such that he later wanted to see the data he felt might support his opinion, Dr. Mitra also conceded that in his professional work he is more careful to check and double-check data. Tr. 762:19–764:4. Because he did not have the data when forming his opinion in this action, Dr. Mitra did not "employ[] ... the same level of intellectual rigor that characterizes the practice of an expert in the field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Dr. Mitra did not even exercise the care customary of his professional work, and his testimony should therefore be stricken as unreliable.

STATEMENT OF FACTS

This case involves a patent pertaining to an ophthalmic composition comprising a compound called moxifloxacin. Teva's claim construction is explained in its concurrently-filed answering brief on non-infringement. However, unless otherwise stated, for the invalidity positions articulated in this brief, Teva addresses Alcon's proposed definition of "moxifloxacin" and "moxifloxacin HCl" (D.I. 79, Exh. 1, ¶¶ 67, 69; Tr. 135:21–25), which have the following names and chemical structures, respectively:



"moxifloxacin" i.e., "moxifloxacin betaine"



Moxifloxacin HCl (hydrochloride), i.e., BAY 12-8039

I. The '830 Patent

Claim 1 of the '830 patent is the only claim asserted against Teva in this case. D.I. 79, Exh. 1, ¶ 77. Claim 1 of the '830 patent is:

> A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt. % and pharmaceutically acceptable vehicle therefor.

PTX. 5, col. 7, ll. 29–32. This claim includes many different types of formulations suitable for ophthalmic use, including solutions, suspensions, ointments, gels, and even sprays. Tr. 186:17–188:9. According to Dr. Loyd Allen, the person of ordinary skill in the art would have viewed the '830 patent as directed to the field of pharmaceuticals, particularly ophthalmic compositions. Tr. 170:10–22. The effective filing date of the '830 patent, for prior art purposes, is September 30, 1998. D.I. 79, Exh. 1, ¶ 18.

The '830 patent does not disclose moxifloxacin HCl, either by name, chemical identifier (i.e., BAY 12-8039), or structure. PTX 5. Dr. Stroman, one of the inventors of the '830 patent (Tr. 622:4-5, PTX 5), testified that he made no effort to ensure that either moxifloxacin HCl or BAY 12-8039 was disclosed in his patent applications that led to the '830 patent, despite his having reviewed the provisional applications before they were filed. Tr. 654:6–655:4, PTX 6.

The '830 patent has four examples, which "are provided to further illustrate the ophthalmic, otic and nasal compositions of the present invention." PTX 5, col. 6, ll. 30–32. These examples, however, are merely ingredient lists and do not contain formulation instructions. In addition to these four examples, the '830 patent also provides lists of suitable preservatives, solubility-enhancing co-solvents, and viscosity enhancing agents. PTX 5, col. 5, l. 66–col. 6, l. 29. Each of these lists is not limited to the agents actually disclosed, but rather includes "other agents known *to those skilled in the art*." PTX 5, col. 6, l. 5; col. 6, ll. 14–15; col. 6, ll. 26–27 (emphasis added). The '830 patent further specifies that its "compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues...." PTX 5, col. 2, ll. 40–43. According to the patent, a pH from 4.5 to 8.0, and an osmolality of 200 to 400 mOsm/kg (preferably 300 mOsm/kg), is acceptable. PTX 5, col. 5, ll. 55–65. Regarding the preservative component, the '830 patent states that "[o]phthalmic, otic and nasal pharmaceutical products are typically packaged in multidose forms." PTX 5, col. 5, ll. 66-67. "Preservatives are thus required to prevent microbial contamination during use." PTX 5, col. 5, l. 67–col. 6, l. 1. Despite these references to the possible components of ophthalmic compositions according to the '830 patent, the patent does not contain any process steps describing *how to make* any ophthalmic composition containing moxifloxacin. PTX 5; Tr. 447:6–22.

The '830 patent also contains MIC data for 10 microorganisms (including *Pseudomonas aeruginosa*[2]) that the patent describes as "commonly associated with ophthalmic, otic and nasal infections...." PTX 5, col. 3, l. 66–col. 4, l. 15; Tr. 660:16–661:4. The data included in the '830 patent were not generated by any of the inventors, nor anyone at Alcon, for that matter. Tr. 661:5–10. In fact, Dr. Stroman testified that these very data came from prior art sources. Tr. 661:5–662:20. The MIC data was included in the patent to, according to Dr. Stroman, "give an idea of the activity of moxifloxacin...." Tr. 661:17–662:3. These data do not reflect the properties of an ophthalmic composition containing moxifloxacin or of any composition claimed in the '830 patent.

II. The '830 Patent's Inventors Filed Provisional Patent Applications In September 1998

A. Alcon's September 1998 Provisional Applications Relating To Moxifloxacin

In September 1998, the inventors of the '830 patent filed provisional applications directed to ophthalmic compositions containing "moxifloxacin". Tr. 573:9–19; PTX 19. The '830 patent is based on these two provisional applications. Tr. 622:4–9, PTX 6. As of September 1998, BAY 12-8039 was the only form of moxifloxacin that Dr. Stroman was aware of. Tr. 658:23–659:13. At the time the provisional applications were filed, Alcon had not conducted any testing on moxifloxacin; in fact, Alcon had not yet received any form of moxifloxacin from Bayer. Tr. 574:2–8. At that time, then, the inventors had not actually made any topical ophthalmic pharmaceutical compositions containing moxifloxacin or a pharmaceutically useful hydrate or salt thereof. Tr. 660:7–15.

[2] *Pseudomonas aeruginosa* was considered in 1998 to be a significant ocular pathogen. Tr. 392:4–22. This is confirmed by the '830 patent. PTX 5, col. 3, l. 65–col. 4, l. 15. Another of the key ocular pathogens discussed extensively at trial was *Staphylococcus aureus*. Tr. 1013:23–1014:1.

B. Alcon's September 1998 Provisional Applications Relating To Other Antibiotics

In September 1998, Alcon also filed provisional applications directed to ophthalmic compositions containing other antibiotics, including other fluoroquinolones. These other applications were essentially the same as the provisional applications for moxifloxacin, even including the same typographical error in Example 3. Tr. 637:10–15. The only significant substantive difference between the various provisional applications is the use of different active antibiotic ingredients, as detailed below. These other applications, also filed on September 30, 1998 by the same inventors of the '830 patent, led to the following:

(1) International Patent Application Publication No. WO/00/18388 ("the '338 publication"), directed to ophthalmic compositions containing trovafloxacin, a fluoroquinolone (see PTX 2025). Tr. 1059:18–1060:23 (Zhanel); PTX 6, BA001-002574; Tr. 622:17–623:17.

(2) International Patent Application Publication No. WO 00/18404 ("the '404 publication"), directed to ophthalmic compositions containing grepafloxacin, also a fluoroquinolone (see PTX 2025). Tr. 630:16–631:3; PTX 6, BA001-2721; Tr. 631:5–18; PTX 6, BA001-002733.

(3) International Patent Application Publication No. WO 00/18387 ("the '387 publication), directed to ophthalmic compositions containing oxazolidinones. Tr. 631:19–623:17; PTX 6, BA001-002555; Tr. 631:19–632:17; PTX 6, BA001-002568.

The specifications of the '388, '404, and '387 publications are nearly identical to that of the '830 patent, but refer to different active agents. For example, the first paragraph under the heading "Background of the Invention" contains the same language in each document:

> The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class

> of [antibiotics].[3] The compositions of the present invention may also contain one or more anti-inflammatory agents.

PTX 5, col. 1, ll. 13–21; PTX 6, BA001-002557 ('387 publication), BA001-002723 ('404 publication); BA001-001-002576 ('388 publication).

As with the '830 patent, each of the three publications also references the same "need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens." PTX 5, col. 1, ll. 49–53; PTX 6, BA001-002557 ('387 publication), BA001-002724 ('404 publication), BA001-002577 ('388 publication).

According to the inventors, the compositions described and claimed in each of these publications can be used in the same manner:

> Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

(PTX 5, col. 2, ll. 23-29; PTX 6, BA001-002559 ('387 publication), BA001-002725 ('404 publication, BA001-002578 ('388 publication)). Also, although different active ingredients are "preferred" in each publication, the possible range of concentration for the active ingredients is the same in each: 0.1 to 1.0 percent by weight. Tr. 634:7–636:23.

Moreover, except for the active ingredients, the four examples provided in the '830 patent and in the '387, '404, and '388 publications are exactly the same, right down to the misspelling of "petrolatum" (as "petrolatium") in Example 3. Tr. 636:24–637:19. For example, the following Example 1, titled "Ophthalmic/Otic/Nasal Solution" is provided in each of them:

---

[3] The phrase "antimicrobial agents known as oxazolidinones" appears in the '387 publication instead of "antibiotics". PTX 6, BA001-002557.

Ingredient	Amount (wt. %)
[active ingredient][4]	0.35
Sodium Acetate	0.03
Acetic Acid	0.04
Mannitol	4.60
EDTA	0.05
Benzalkonium Chloride	0.006
Water	q.s. 100

III. The Inventors Of The '830 Patent Learned Of Moxifloxacin HCl From The Prior Art

The inventors listed on the '830 patent did not invent moxifloxacin or a salt or hydrate thereof. Rather, the inventors learned of this compound and its properties, particularly moxifloxacin HCl, from others. Tr. 568:12–569:6, 571:2–20.

A. Moxifloxacin HCl Was Developed By Bayer And Publicized As An Antibiotic In 1996 and 1997, Well Before The Priority Date Of The '830 Patent

Bayer Pharmaceuticals Corp. is the holder of a FDA-approved New Drug Application for a composition sold under the trade name Avelox®. D.I. 79, Exh. 1, ¶ 27. Bayer lists U.S. Patent Nos. 4,990,517 and 5,607,942 in the FDA's Orange Book as covering its Avelox® product. *Id.* The '942 patent issued on March 4, 1997. PTX 3. Claim 1 of the '942 patent provides the chemical structure for moxifloxacin, but the word "moxifloxacin" does not appear in the '942 patent. Tr. 176:22–177:3. The issuance of the '942 patent (March 4, 1997) predates the effective filing date (September 30, 1998) of the application for the '830 patent by over a year and a half. See D.I. 79, Exh. 1, ¶ 18.

According to the '942 patent, the compounds disclosed therein have antibacterial properties, and are "active against a very broad spectrum of microorganisms." PTX 3, col. 53, ll. 34–35). Additionally, before September 1998, Bayer publicized the antibacterial properties of

[4] In the '830 patent, the active ingredient is "Moxifloxacin." PTX 5, col. 6, ll. 34–47. In the '387 publication, the active ingredient is "Oxazolidinone." PTX 6, BA001-002566. In the '404 publication, the active ingredient is "Grepafloxacin." PTX 6, BA001-002733. In the '388 publication, the active ingredient is "Trovafloxacin." PTX 6, BA001-002586.

moxifloxacin HCl through peer-reviewed literature and scientific conferences. For example, in 1996, Bayer scientists published an article on the "In Vitro Activity of BAY 12-8039, a New 8-Methoxyquinolone." PTX 1124. Bayer scientists also presented a poster (PTX 1098) and abstract (PTX 115) illustrating the "Synthesis and In Vitro Activity of BAY 12-8039, a New 8-Methoxyquinolone" as early as the 1996 Interscience Conference on Antimicrobial Agents and Chemotherapy ("ICAAC"). The poster and abstract included information only about BAY 12-8039. PTX 115, PTX 1098. The disclosed information is relevant to the formulation of ophthalmic compositions, including the activity, solubility, and toxicity of BAY 12-8039. Tr. 223:17–226:8.

B. Alcon Was Motivated To Use Moxifloxacin HCl In An Ophthalmic Composition By Bayer's 1997 Publications

Dr. Stroman has been employed by Alcon since 1990 and is currently the director of Alcon's Anti-Infective Program. Tr. 565:1–18. Dr. Stroman's responsibilities included the identification and screening of compounds that might be appropriate for use in treating ophthalmic and otic infections. Tr. 565:8–18.

Dr. Stroman testified that, in 1998, Alcon was actively searching for compounds that improved on the two state-of-the art products at that time for the treatment of ophthalmic infections, Ciloxan® and Ocuflox®. Tr. 568:12–569:6. Dr. Stroman identified moxifloxacin as a compound he was interested in testing based on Bayer's presentation at the 1997 ICAAC conference. Tr. 571:2–20. Dr. Stroman acknowledged that he saw Bayer's presentation on the "Synthesis and In Vitro Activity of BAY 12-8039, a New 8-Methoxyquinolone," i.e., PTX 1098 (Tr. 640:22–641:1), and that it was the MIC data presented in the 1997 ICAAC poster for

BAY 12-8039, particularly as compared to ciprofloxacin,[5] which motivated Dr. Stroman to seek to develop BAY 12-8039 for topical ophthalmic use. Tr. 571:2–19.

C. Alcon Requested Moxifloxacin HCl from Bayer In February 1998

After Dr. Stroman saw the information Bayer presented on BAY 12-8039 (moxifloxacin HCl) in 1997, he sought to obtain a sample of this molecule from Bayer. Tr. 645:21–24. Dr. Stroman expected that he would be able to obtain BAY 12-8039 from Bayer because of Alcon's ongoing relationship with Bayer. Tr. 571:2–19.[6] To this end, on February 10, 1998, Dr. Stroman submitted an "Alcon Research Compound Request" for BAY 12-8039. PTX 1065; Tr. 646:15–22. Dr. Stroman identified the compound he wanted as BAY 12-8039, identified the source as Bayer, and indicated that he had seen information about the compound on several posters shown at the 1997 ICAAC. PTX 1065; Tr. 646:15–22. Dr. Stroman also initialed the Request before submitting it and before receiving BAY 12-8039 from Bayer. Tr. 648:9–14. However, Alcon would not receive any BAY 12-8039 from Bayer for nearly a year following Dr. Stroman's initial, February 1998, request.

D. The Inventors Of The '830 Patent Decided To Obtain And Develop Ophthalmic Moxifloxacin HCl In The Summer Of 1998

On September 18, 1998, also before Alcon ever received any compound to test, Dr. Robert Abshire, another of the inventors of the '830 patent (Tr. 643:19–21) announced the tremendous potential of moxifloxacin to Alcon. DTX 64. After referencing the potential for a

[5] Ciprofloxacin, like moxifloxacin, is a fluoroquinolone. Tr. 172:20–24.

[6] Consistent with Alcon's strategy to follow systemic drugs into the ophthalmic marketplace (DTX 68; Tr. 669:11–671:4), Alcon had previously licensed ciprofloxacin from Bayer (previously marked as a tablet (Cipro®) by Bayer) and had developed it into an ophthalmic composition (Ciloxan®). Tr. 571:20–572:2; 666:14–667:11; DTX 144. In 1998, Ciloxan® had come to represent the gold standard for topical ophthalmic antibiotics. Tr. 459:8–22. However, in 1998, Alcon became concerned that Bayer's patent on ciprofloxacin would soon expire and was thus motivated to seek a replacement product (DTX 69; Tr. 671:9–673:2).

licensing agreement with Bayer for moxifloxacin, Dr. Abshire said "I do think that upper level management may have received the golden goose on a silver platter." DTX 64. Dr. Abshire also stated that both he and Dr. Stroman had agreed that Alcon "should obtain moxifloxacin and develop it for ophthalmic use." DTX 64; Tr. 644:1–5.

Dr. Abshire also referenced data showing that moxifloxacin was less active than ciprofloxacin *in vitro* against one key ophthalmic pathogen, *Pseudomonas aeruginosa*. DTX 64. However, Dr. Abshire did not "think this will make a difference in its clinical efficacy, i.e. it will handle an eye infection with this organism as readily as will ciprofloxacin." DTX 64.

Dr. Abshire's September 1998 email also stated that Dr. Cagle, a co-inventor of the '830 patent, had expressed that he "would like to try to have a once-a-day dosing regimen for conjunctivitis." DTX 64. Dr. Cagle's interest in moxifloxacin was further motivated by market pressures. As shown by an email Dr. Cagle wrote on June 24, 1999, he was concerned with finding a replacement for ciprofloxacin because the patent on ciprofloxacin was going to expire in the "2003 +/– timeframe". DTX 69; Tr. 671:9–673:2.[7]

IV. Alcon Did Not Test Moxifloxacin HCl Until 1999

Alcon did not receive a sample of moxifloxacin HCl until January 4, 1999, well after Alcon filed its provisional applications on ophthalmic "moxifloxacin" compositions. Tr. 648:11–649:11. Before this time, no one at Alcon had conducted any testing on moxifloxacin. Tr. 650:10–18. In fact, internal Alcon records show that, as of February 9, 1999, in the context of moxifloxacin formulation development, Alcon was "[n]ot considering anything novel in first 3

[7] Dr. Cagle's email, predating this action by almost a decade, did not reference any of the purported deficiencies in Ciloxan® to which Alcon's experts, Drs. Alfonso and Zhanel, testified at trial. DTX 69; Tr. 671:9–673:2. This should underscore their opinions as litigation inspired and not reflective of real world practical reality.

months of this evaluation since we will need to share with Bayer all findings and test results." PTX 1066; AL001-00214.

Alcon tested moxifloxacin HCl only after it received it from Bayer in January 1999. Until this action commenced,[8] Alcon received and tested only "Moxifloxacin HCl [BAY 12-8039]." PTX 363, AL003-00163 (bracketed text in original); Tr. 655:5–12, 658:9–22.

V. Moxifloxacin Betaine And Moxifloxacin HCl Are Different Chemicals

As Dr. Taylor testified, moxifloxacin betaine is a different compound from moxifloxacin HCl. Tr. 134:23–135:25. In comparing moxifloxacin betaine to moxifloxacin HCl, Dr. Taylor testified that "It's a different solid. *It has different characteristics*. It has a different melting point. It's an individual compound in its own right." Tr. 135:12–25 (emphasis added). That moxifloxacin HCl and moxifloxacin betaine are distinct compounds is further supported by the fact that the Chemical Abstract Service provides different identification numbers for these two compounds. Tr. 134:5–134:25; PTX 550.

The different properties of moxifloxacin HCl and moxifloxacin betaine are pertinent to the formulation of ophthalmic moxifloxacin compositions. As Dr. Taylor testified, using one or the other can have an effect on the pH of the resulting solution. Tr. 95:6–13. Dr. Taylor also testified that hydrochloride salts are "known and prepared not only because of their convenience in preparation, their storage capabilities, their stabilities and the like but also *for their solubilities*." Tr. 143:15–22 (emphasis added).

The testimony provided to this Court in *Bayer AG v. Dr. Reddy's Labs., Ltd.* (Civil Action No. 04-179-SLR) by Dr. Uwe Petersen, one of the inventors of Bayer's '942 patent, confirms that the differences between moxifloxacin betaine and moxifloxacin HCl have an

[8] Alcon first asked Bayer for, and first received, moxifloxacin *betaine* only in December 2007, in connection with this litigation. Tr. 678:7–679:21.

additional direct effect on the pharmaceutical uses of those compounds. When asked to explain Bayer's test results for moxifloxacin betaine, Dr. Petersen stated that the betaine

> is not good tolerated, because 200 milligrams, all the mice in this experiment died. It was lethal. Therefore, we had no further interest in this compound.

Trial Transcript, *Bayer AG et al. v. Dr. Reddy's Labs., Ltd.*, C.A. 04-179-SLR, pp. 313:12–314:1 (Aug. 8, 2006). Plainly, BAY 12-8039 was much safer than moxifloxacin betaine. As Bayer's development and commercialization of Avelox®, which contains BAY 12-8039, shows in contrast with the betaine, Bayer certainly did have further interest in the HCl salt, BAY 12-8039.

VI. The Prior Art To The '830 Patent

The prior art that is pertinent to the '830 patent includes: (1) prior art relating to ophthalmic antibiotic compositions; and (2) prior art relating to moxifloxacin, particularly moxifloxacin HCl (i.e., BAY 12-8039).

A. The Prior Art Relating To Ophthalmic Antibiotic Compositions

As of September 1998 the use of antibiotic compounds, including fluoroquinolones, in ophthalmic compositions was well known. As of 1998, fluoroquinolones were known to be effective broad spectrum antibiotics. Tr. 173:23–25. Indeed, the two state-of-the-art ophthalmic compositions in September 1998 for the treatment and prevention of ophthalmic infections, identified by Drs. Stroman and Alfonso, were Ciloxan® and Ocuflox® (Tr. 568:12–24, 459:8–22), both of which contained fluoroquinolones as the active pharmaceutical ingredient.[9]

In addition to these products, the prior art also included ophthalmic compositions containing the aminoglycoside, tobramycin. Tr. 208:16–23. The prior art also included Alcon's

[9] The active ingredient in Ciloxan® is ciprofloxacin (Tr. 194:9–12, 568:16–17, 467:1–17, 856:8–13)), while the active ingredient in Ocuflox® is ofloxacin (Tr. 220:14–20, 568:18–19, 478:21–22, 856:8–13). Ciprofloxacin and ofloxacin are both fluoroquinolones. Tr. 172:20–24, 391:12–392:2, 856:8–13.

U.S. Patent No. 5,149,693, which also discloses ophthalmic antibiotic compositions containing tobramycin. DTX 78; Tr. 213:4–14.

1. Ciloxan® Ophthalmic Solution And Ointment

Ciloxan® ophthalmic solution was approved by the FDA on December 31, 1990. DTX 141; Tr. 195:3–10. Ciloxan® ophthalmic solution contains 0.35 weight percent of ciprofloxacin hydrochloride as the active ingredient. DTX 144; Tr. 194:13–18. Ciloxan® ophthalmic solution also contains, as inactive ingredients: benzalkonium chloride 0.006% (as a preservative); sodium acetate and acetic acid (as a buffer); mannitol 4.6% (to adjust tonicity); edetate disodium 0.05% (as a preservative enhancer); hydrochloric acid and/or sodium hydroxide (to adjust pH to about 4.5); and water. DTX 144; Tr. 195:11–196:2.

As of 1998, Ciloxan® was also marketed by Alcon as an ophthalmic ointment. PTX 1063; Tr. 202:11–17. This composition was approved by the FDA on March 30, 1998. PTX 146; Tr. 203:6–17. Ciloxan® ointment contains 0.3 weight percent of ciprofloxacin hydrochloride as the active ingredient. PTX 1063; Tr. 202:11–203:3. The inactive ingredients in Ciloxan® ointment are mineral oil and white petrolatum. PTX 1063; Tr. 202:11–203:5.

2. Ocuflox® Ophthalmic Solution

Ocuflox® is marketed by Alcon's competitor, Allergan, Inc. DTX 159; Tr. 220:21–24. Ocuflox® was marketed as of 1995. DTX 159. Ocuflox® contains 0.3 weight percent of ofloxacin as its active ingredient. DTX 159; Tr. 220:25–221:8. The inactive ingredients in Ocuflox® are benzalkonium chloride (0.005%), sodium chloride, and purified water; it may also contain hydrochloric acid or sodium hydroxide to adjust the pH to about 6.4. DTX 159; Tr. 220:25–221:8.

3. Tobradex® Ophthalmic Suspension

Tobradex® ophthalmic suspension is an antibiotic composition that contains the aminoglycoside antibiotic tobramycin. DTX 145; Tr. 207:12–14, 208:16–23. Tobradex® ophthalmic suspension is manufactured by Alcon. DTX 145; Tr. 208:16–19. It was marketed as of 1996. See DTX 145.

The active ingredients in Tobradex® ophthalmic suspension are tobramycin (0.3%) and dexamethasone (0.1%), an anti-inflammatory. DTX 145; Tr. 208:20–23. The inactive ingredients in Tobradex® ophthalmic suspension are: tyloxapol, (as a wetting agent with surface active properties); benzalkonium chloride, 0.01% (as a preservative); edetate disodium (as a preservative enhancer); sodium hydroxide (to adjust tonicity); hydroxyl ethylcellulose (to adjust viscosity); sodium sulfate, sulfuric acid, and/or sodium hydroxide; and water. DTX 145; Tr. 208:24–209:16.

4. U.S. Patent No. 5,149,693 (Cagle, et al.)

U.S. Patent No. 5,149,693 is titled "Combination of Tobramycin and Fluorometholone for Topical Ophthalmic Use." DTX 78. It issued on September 22, 1992, and is assigned to Alcon. DTX 78; Tr. 213:4–14. Example II of the '693 patent is:

Flurometholone acetate, USP	0.1% + 2% excess	1 mg + 2% excess
Tobrmaycin; Micronized, USP	0.3% + 7% excess	3 mg + 7% excess
Chlorobutanol, Anhydrous, NF	0.5% + 25% excess	5 mg + 15% excess
Mineral Oil, USP	5%	50 mg
White Petrolatum, USP	QS 100%	QS 1 g

DTX 78, col. 2, ll. 60–65.

B. The Prior Art Relating To Moxifloxacin HCl

The prior art was also replete with information on moxifloxacin HCl. Indeed, the prior art available was encouraging. Bayer had published much information about moxifloxacin

HCl's characteristics, including its antibacterial activity, resistance profile, toxicity profile, and pharmacokinetics.

1. Moxifloxacin HCl Was Known In September 1998 To Have Antibacterial Activity

By September 1998, moxifloxacin HCl was known to have antibacterial activity. For example, the poster Dr. Stroman saw at the 1997 ICAAC showed that moxifloxacin HCl had a lower MIC against *Pseudomonas aeruginosa* than that of ofloxacin. DTX 4017; Tr. 477:18–479:6. This poster also showed that moxifloxacin HCl had a lower MIC against *Staphylococcus aureus* than ofloxacin. DTX 4017; Tr. 477:18–478:10. Other scientific literature sponsored by Bayer and available in 1998 showed the MIC value of moxifloxacin HCl to be lower than that of ciprofloxacin against ciprofloxacin- and methicillin-resistant *Staphylococcus aureus*. PTX 1124; Tr. 479:19–481:5. It was also known in September 1998 that moxifloxacin HCl had antibacterial activity against classes of bacteria associated with ophthalmic infections. Tr. 495:2–13.

The prior art '942 patent also provided a person of ordinary skill with the expectation that moxifloxacin would be effective against ophthalmic pathogens. For example, the '942 patent specifically points out that the compounds disclosed therein can prevent, alleviate, or cure, *inter alia*, eye infections. Tr. 179:16–180:10; PTX 3, col. 54, ll. 1–22.

2. Moxifloxacin HCl Was Known In September 1998 To Have A Better Resistance Profile Than Ciprofloxacin

According to Dr. Alfonso, the development of resistance to fluoroquinolones by bacteria (i.e., the compound's "resistance profile") was a known problem in September 1998. Tr. 419:11–420:2. However, publications as of 1998 reveal that moxifloxacin HCl was known to be less prone to the development of bacterial resistance than ciprofloxacin. See PTX 1124, PTX 1125, Tr. 520:24–522:25, 1045:23–1047:2, 525:21–526:13.

For example, a 1996 article published by Bayer scientists reported that resistance against moxifloxacin HCl developed much less readily in gram-negative bacteria[10] than did resistance against ciprofloxacin. PTX 1124, p. 424; Tr. 520:24–522:25. This same article also particularly reported that resistance to moxifloxacin HCl in *Pseudomonas aeruginosa* and *Staphylococcus aureus* emerged less rapidly than resistance to ciprofloxacin. PTX 1124, p. 422; Tr. 1045:23–1047:2. Another article available in September 1998 reported that, with respect to *Staphylococcus aureus* and as compared to older fluoroquinolones like ciprofloxacin and ofloxacin - both of which were state-of-the-art topical ophthalmic antibiotics - moxifloxacin HCl was less influenced by known mutations within the genetic loci involved in fluoroquinolone resistance. PTX 1125, p. 484; Tr. 525:21–526:13.

3. Moxifloxacin HCl Had Not Demonstrated Unacceptable Toxicity As Of September 1998

As of September 1998 the prior art showed that moxifloxacin HCl had not demonstrated unacceptable toxicity. For example, a June 1998 article, co-authored by Bayer scientists, reported moxifloxacin HCl to be a compound with a low level of toxicity, with single systemic doses of up to 800 mg being tolerated without significant side effects. DTX 195, p. 1399; Tr. 528:2–529:20. The exposure to moxifloxacin from such a dose is much higher than from an ophthalmic dose; indeed, exposure to Vigamox® three times daily results in systemic exposure to moxifloxacin HCl that is 1,600 to 1,000 times lower than the exposure from even a 400 mg oral dose. Tr. 540:17–541:10.

The Bayer poster at the 1997 ICAAC also stated that moxifloxacin HCl had entered Phase II clinical trials. PTX 1098; Tr. 225:19–226:21. Phase I clinical studies are particularly

[10] *Pseudomonas aeruginosa* is a gram-negative bacteria; *Staphylococcus aureus* is a gram-positive bacteria. (Tr. 477:10–15).

focused on determining whether a drug is toxic, and are generally required before a compound can begin Phase II studies. Tr. 226:9–227:7. What is more, Bayer scientists advised the U.S. Patent Office that moxifloxacin HCl had a "good pharmacological profile, good activity, and *good tolerability*...." Tr. 182:9–184:24 (emphasis added); PTX 4, BL002-001721–35.

4. Pharmacokinetic Data Available In September 1998 Indicated Moxifloxacin HCl Could Be Formulated Into A Topical Ophthalmic Pharmaceutical Composition

It is not possible to know the ocular pharmacokinetics of a composition before making a composition and testing it. Tr. 766:8–10, 510:23–512:16. Nonetheless, certain parameters, such as solubility of the active ingredient, can affect an ophthalmic formulation's pharmacokinetics. Tr. 512:17–21. Indeed, Dr. Allen testified that the first piece of information a person making an ophthalmic formulation of a new drug would want to know would be that drug's solubility, because solubility influences the dosage form. Tr. 172:2–11. The solubility of moxifloxacin HCl in water was known in 1998, and was provided on the very poster that Dr. Stroman viewed at the 1997 ICAAC. Tr. 512:22–513:21, 223:21–225:18. The solubility reported (24 mg/mL) would have informed a person of ordinary skill in the art that moxifloxacin HCl could be made into a solution. Tr. 224:4–10.

Additionally, the pharmacokinetics of moxifloxacin HCl had been reported by September 1998. For example, in August 1998 Bayer scientists reported that "moxifloxacin is rapidly bactericidal and effectively penetrates extravascular tissue, including lung tissue." PTX 223, p. 2060; Tr. 513:22–515:13. The eye, like the lung, is an extravascular tissue. Tr. 515:14–20. Other prior art available in September 1998 showed that moxifloxacin HCl effectively penetrates the cerebrospinal fluid. DTX 191; Tr. 517:3–518:17. This is especially pertinent to ophthalmic formulations, as, according to Alcon's own expert, the brain and the eye are the two most protected organs in the body. Tr. 518:15–21. Indeed, Dr. Mitra conceded that a

person of ordinary skill in the art would have expected in 1998 that moxifloxacin would penetrate ocular tissue, and would more readily penetrate the eye than ofloxacin (Tr. 786:21–787:18), which was state-of-the-art in 1998 for use as a topical ophthalmic antibiotic. Tr. 568:12–24, 459:8–22.

VII. Vigamox®

Vigamox® is a topical ophthalmic pharmaceutical solution marketed by Alcon. DTX 137; Tr. 1085:11–12. The active ingredient in Vigamox® is moxifloxacin HCl (0.5 weight percent). DTX 137; Tr. 174:1–11. Vigamox® is packaged in a container holding multiple doses of the composition. Tr. 1004:18–20.

The FDA has approved Vigamox® only for the treatment of conjunctivitis, and Vigamox® is indicated only for the treatment of conjunctivitis. Tr. 541:17–19. Vigamox® is not FDA-approved for the treatment of keratitis, nor for prophylactic treatment. Tr. 542:12–24. Vigamox® is not even FDA-approved for the treatment of any infections caused by *Pseudomonas aeruginosa*. Tr. 543:1–8. Unquestionably, though, the FDA approved Vigamox®. Tr. 543:9–11.

The '830 patent does not describe the composition of Vigamox®. Tr. 1004:15–17, 673:16–674:3. According to Dr. Stroman, Vigamox® is an optimized solution (Tr. 674:4–7), that is "one that is going to give you the desired therapeutic level for the desired length of time inside the eye and in the various eye structures." Tr. 767:9–13. None of the inventors of the '830 patent were involved with the optimization of Vigamox®. Tr. 674:4–13. The Vigamox® formulation, thus, was created by persons other than the inventors of the '830 patent.

ARGUMENT

I. Claim 1 Of The '830 Patent Is Invalid In Light Of The Prior Art If Alcon's Proposed Claim Construction Is Adopted

If the Court construes "moxifloxacin" as Teva contends, then the Court need not reach Teva's § 102 and § 103 defenses, and the bulk of Dr. Allen's, Dr. Alfonso's, and Dr. Zhanel's testimony, and all of Dr. Mitra's testimony, is moot. If, however, the Court construes "moxifloxacin" as Alcon contends, then, for the reasons explained below, claim 1 is invalid as obvious in light of, and as anticipated by, the prior art.

A. Claim 1 Of The '830 Patent Is Obvious In Light Of The Prior Art

Assuming that claim 1 of the '830 patent is construed as Alcon contends it should be, claim 1 of the '830 patent would have been obvious to a person of ordinary skill in the art in September 1998, in view of the prior art. The Federal Circuit's analysis in its recent decision in *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254 (Fed. Cir. 2007), *cert. denied*, 128 S. Ct. 1259 (2008), is persuasive in this case. In *Daiichi*, the Federal Circuit held that a claim covering the use of one fluoroquinolone in a method of treating ear infections was obvious in light of the prior art use of another fluoroquinolone to treat ear infections. *Id.* at 1258–59. The facts on which the *Daiichi* Court based its finding of obviousness are very similar to the facts of this case, and compel the legal conclusion that claim 1 of the '830 patent would have been obvious.

1. The Law Relating To Obviousness

Under 35 U.S.C. § 103(a) a patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The Supreme Court has provided the following guidance for the obviousness inquiry:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17–18 (1966). If, after conducting this analysis, this Court concludes that claim 1 would have been obvious at the time the invention was made, then the claim is invalid. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). Because "progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts." *Id.* at 1746 (citing U.S. Const., Art. I, § 8, cl. 8). "Obviousness does not require absolute predictability." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The Court need not find an explicit teaching, suggestion or motivation in the prior art to combine the elements of claim 1 of the '830 patent as a predicate to finding it to be obvious. *KSR*, 127 S.Ct. at 1741.

2. The *Graham* Factors

a. The Person Of Ordinary Skill Has An Entry-Level Degree In Pharmacy And 5 To 10 Years Of Experience Formulating Ophthalmic Compositions

As Dr. Loyd Allen testified, the person of ordinary skill in the art to which the subject matter of the '830 patent is directed is an individual with an entry-level degree in pharmacy with 5 to 10 years of experience in ophthalmic formulation. Tr. 171:9–14, 245:17–246:8. Dr. Allen is an expert in drug formulation and pharmaceutics, which is the science of creating drug dosage forms based on a drug's chemical characteristics. Tr. 167:12–23. Dr. Allen was the only expert at trial able to provide a clear definition of a person who can actually practice the invention of the '830 patent without undue experimentation. The Court should accept Dr. Allen's definition.

i. The Factors Useful In Determining The Level Of Ordinary Skill In The Art Support Dr. Allen's Definition

> Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.

Daiichi, 501 F.3d at 1256 (quoting *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983)). "These factors are not exhaustive but are merely a guide to determining the level of ordinary skill in the art." *Id.* Furthermore, Judge Farnan recently recognized that these "factors need not be present in every case and certain factors may be more predominant in some cases than in others." *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 536 F. Supp. 2d 476, 492 (D. Del. 2008). Each of these factors supports Dr. Allen's opinion in this case.

As to the first *Daiichi* factor, the inventors have academic degrees in microbiology, but they drew on virtually none of their formal, microbiological, education to "invent" the subject matter of the '830 patent. There simply is no dispute here that none of them conducted any microbiological tests of, nor work with, moxifloxacin (betaine or HCl) prior to filing their 1998 patent applications. Nor does the '830 patent contain any record of any microbiological tests of topical, ophthalmic moxifloxacin. Thus, the formal education of the inventors as microbiologists was and is immaterial. It is perhaps more revealing that the education of the inventors actually is inconsistent with Alcon's position and Alcon's experts, who all agree that *medical* education and training in ophthalmology also is within the level of ordinary skill (Tr. 406:1–407:2; 988:18–989:5). Of course, none of the inventors has such education or training.

Instructively, the inventors, were long-time Alcon employees were privy to Alcon's vast know-how in the development of ophthalmic formulations and knew it had long been Alcon's business model to formulate known drugs for ophthalmic use (DTX 68, Tr. 669:11–670:4). This

professional experience must also be regarded as part of their education, and it enabled them to simply cobble the formulations disclosed in the '830 patent from prior optimized formulations of other drugs (e.g., Alcon's Ciloxan® fluoroquinolone formulations). Optimization of such formulations is *not* within the skill of the inventors (Tr. 675:4–13), is not within the skill of a microbiologist, such as Dr. Zhanel (Tr. 1002:18–1003:16, 1077:18–1078:3), and is not within the skill of an ophthalmologist, such as Dr. Alfonso (Tr. 446:12–15). Thus, that the inventors – microbiologists all[11] – merely cribbed the work of experienced formulators' prior art formulations for purposes of the '830 patent reveals that their patent relies on the training of persons other than themselves and specifically the experienced formulators such as from whom they mimicked the '830 patent's Examples.

As to the second *Daiichi* factor, the '830 patent itself points out that the type of "problem" encountered in the art, and thus to which the claimed subject matter of the '830 patent pertains, was formulating an antibiotic compound into a topical ophthalmic composition. PTX 5, col. 2, ll. 38–45; Tr. 248:5–23. Solving this "problem" was the very heart of Alcon's business model. DTX 68, Tr. 669:11–670:4. For example, Alcon developed its Ciloxan® ophthalmic products only after ciprofloxacin was available in systemic formulations, such as tablets. Tr. 666:14–668:7.

Regarding the third *Daiichi* factor, both Ciloxan® solution and ointment represented favorable, commercially accepted prior art solutions to the ongoing "problem," of formulating an ophthalmic composition of a known fluoroquinolone antibiotic. Tr. 666:14–667:11; DTX 144, PTX 1063. Not only were these two prior art formulations merely topical reformulations of a

[11] Dr. Allen's definition does not actually exclude the person of ordinary skill from having some skill and experience in microbiology. Tr. 246:9–18. That the inventors are microbiologists able to incorporate the work of experienced formulators supports his opinion.

fluoroquinolone previously developed for systemic use, Ciloxan® solution was considered state-of-the-art in 1998. The Federal Circuit has held obvious and unpatentable the substitution of one fluoroquinolone for another for the topical treatment of infection. *Daiichi*, 501 F.3d at 1258. (Otic ofloxacin was obvious in light of prior otic ciprofloxacin.)

As to the fourth *Daiichi* factor, innovations in ophthalmic solutions of known systemically-useful antibiotics follow rapidly, as it is generally not difficult to formulate known antibiotics into ophthalmic formulations. Tr. 233:20–234:6. The development of topical ophthalmic dosage forms containing an antibiotic after the development of corresponding systemic dosage forms, like tablets, is "routine." Tr. 231:24–232:16. In fact, it is unrebutted that the four exemplary formulations in the '830 patent merely cobble prior art formulations and were copied with no experimentation whatsoever. Tr. 196:7–197:18, 204:15–205:16, 209:24–211:13, 214:15–18, 648:11–649:11, 649:10–13; DTX 4013; DTX 4014; DTX 4015; DTX 4016.

As to the fifth *Daiichi* factor, it is undisputed that topical ophthalmic pharmaceutical compositions must be made in such a way that they are sterile, non-irritating, convenient to administer, stable, and such that the vehicle is non-toxic. Tr. 275:18–277:3. Formulation of topical ophthalmic compositions requires the special skills of a person with knowledge and experience in drug formulation and pharmaceutics to achieve these goals. This relates to the discussion above *re* the first *Daiichi* factor inasmuch as Alcon's only expert microbiologist, Dr. Zhanel, testified that he and his laboratory colleagues might be able to prepare certain "microbiological" formulations of antibiotics, but that such formulations should certainly never be allowed to be placed in the eyes. Tr. 992:11–993:22; 1004:3–14.[12]

[12] Dr. Zhanel deferred to Teva's expert's, Dr. Allen's, expertise in pharmaceutical compounding and manufacturing matters. Tr. 1002:18–1003:16, 1077:18–1078:3.

The final *Daiichi* factor also supports Teva's definition. Education and experience in pharmaceutics and drug formulation is necessary to understand what it takes for a composition to be a suitable ophthalmic formulation. Tr. 369:4–370:3. Without such qualifications, a person would be unable to use the teachings of the '830 patent, which completely lacks any disclosure of formulation process methodology, to make an ophthalmic pharmaceutical composition containing moxifloxacin that is suitable for administration to a patient. Further, as explained below, Alcon's experts do not have sufficient expertise in formulation to practice the subject matter of claim 1 of the '830 patent. See, e.g., Tr. 449:18–450:24, Tr. 452:5–23, Tr. 453:4–455:7, Tr. 1002:18–1003:16, 1077:18–1078:3.

Also, in its most recent decision involving similar technology, the Federal Circuit held that the level of ordinary skill was that of a person engaged in formulating fluoroquinolone pharmaceuticals for topical application. *Daiichi*, 501 F.3d at 1258 (there, a formulation for use in a method of treating the ear, here, a formulation for the eye).

ii. The Specification Of The '830 Patent Supports Dr. Allen's Definition

The '830 patent's specification confirms that the person of ordinary skill in the art must be a person with formulation experience. First, the "Background of the Invention" states that the "invention is directed to the *provision of topical antibiotic pharmaceutical compositions* for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections...." PTX 5, col. 1, ll. 13–16 (emphasis adeed). "Providing compositions" is precisely what a compounding pharmacist does. Tr. 233:20–234:6. The "Summary of the Invention" further focuses on the special characteristics of compositions of the patent, stating that such "compositions of the present invention are specially *formulated* for topical application to ophthalmic, otic and nasal tissues." PTX 5, col. 2, ll. 38–40 (emphasis added).

The '830 patent goes on to disclose four specific examples of compositions that "further illustrate the ophthalmic, otic and nasal *compositions of the present invention*." PTX 5, col. 6, l. 30–col. 7, l. 23 (emphasis added). The patent provides no process steps describing how to make any of these examples. PTX 5; Tr. 447:6–22. The patent also sets forth examples of preservatives, solubility enhancing agents, and viscosity enhancing agents which are suitable for use in accordance with the '830 patent. PTX 5, col. 5, l. 66–col. 6, l. 29. For each of these categories the patent states that "other agents known to those skilled in the art," may also be used. PTX 5, col. 5, l. 66–col. 6, l. 29. Similarly, the specification ends with the statement that the invention is not limited to the examples provided because "obvious variations thereon will become apparent *to those skilled in the art*." PTX 5, col. 7, ll. 25–26 (emphasis added).

The patent's references to the presumed knowledge of those skilled in the art shows that different ingredients should be used depending on the nature of the use for any particular formulation. This provides a clear indication that the patent is directed to those individuals who have knowledge and experience sufficient to fill in the gaps, i.e., by using appropriate compounding excipients to allow them to formulate ophthalmic compositions. Dr. Allen testified that this is the type of work that compounding pharmacists do "every day" (Tr. 233:20–234:6), while Alcon has no evidence that microbiologists and/or ophthamologists would have knowledge of such matters remotely similar to a pharmacist skilled in ophthamological formulation. Thus, education, experience, and skill in pharmaceutics and formulation are required to create suitable ophthalmic compositions, which ophthalmologists or microbiologists generally lack.

Dr. Allen's definition of a person of ordinary skill in the art is the only definition that fills in the gaps in the '830 patent's disclosure and which is tied to what the patent claims (a

composition), what it states in the title as the invention (a composition), what is referred to in the patent as within the ordinary skill (the selecting of excipients), and what is necessary to fill in the gaps of the patent (lack of teaching of formulation process). Accordingly, unless the person of ordinary skill has the knowledge and experience described by Dr. Allen, the patent would not enable the invention, as explained below.

iii. Alcon's Definitions Of A Person Of Ordinary Skill Are Contradictory And Not Helpful To The Court

Alcon now asserts that a person of ordinary skill "would have a Ph.D. in microbiology ***and/or*** an M.D. degree with training in ophthalmology." AB, p. 6.[13] "And/or" is problematic and unhelpful. By refusing to define precisely who the person of ordinary skill in the art is, and instead using the indefinite "and/or" connector, Alcon fails to provide the Court with a cogent lens through which to view the patent and the prior art, the very reason for the "person of ordinary skill in the art" standard. *Cf. DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361–63 (Fed. Cir. 2006); *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

Alcon's ambiguous definition of a person of ordinary skill in the art is but an attempt to conceal the fact that Alcon's own experts' testimony is inconsistent. Dr. Alfonso testified that the person of ordinary skill in the art is a "microbiologist and/or ophthalmologist with Ph.D. and/or M.D.," with various experiences and knowledge (PTX 2018; Tr. 406:12–407:2, 444:14–445:3), but even Dr. Alfonso agrees that not every microbiologist would be a person of ordinary skill in the art (Tr. 445:10–20). Dr. Zhanel also testified that a person of ordinary skill is a "microbiologist and/or an ophthalmologist." Tr. 988:18–989:5. Drs. Taylor and Mitra merely

[13] "AB" (Alcon's Brief) refers to Plaintiff's Post-Trial Brief On Infringement (D.I. 93).

assumed that Dr. Alfonso's definition was correct and have no independent opinions. Tr. 51:10–16, 696:20–697:3.

Neither Dr. Alfonso nor Dr. Zhanel has the requisite qualifications to testify as a person of ordinary skill under Alcon's broad definition. Dr. Alfonso does not have a Ph.D. (Tr. 444:14–446:1) and therefore cannot be a person with "a Ph.D. in microbiology." Similarly, Dr. Zhanel is not a medical doctor (Tr. 987:25–988:9), and thus cannot have "an M.D. degree with training in ophthalmology." To the extent that the person of ordinary skill in the art is a microbiologist **and** an ophthalmologist, Alcon has presented no expert competent to testify from that perspective. To the extent that the person of ordinary skill in the art is a microbiologist **or** an ophthalmologist, then either Dr. Zhanel or Dr. Alfonso (but certainly one of the them, and also certainly the chemist, Dr. Taylor), is not competent to testify on the obviousness and enablement of claim 1. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 347 F.3d 1367, 1371–1372 (Fed. Cir. 2003) (discounting an expert's testimony as to how a person of ordinary skill in the art would read the patent where the expert was a chemist who was not qualified in pharmacology, the field of the invention); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 489 (D. Del. 2006), *aff'd,* 501 F.3d 1263 (Fed. Cir. 2007) (expert testimony is "of limited value" when the expert is not qualified to speak from the perspective of a person having ordinary skill in the art); *see also In re Luvisi*, 342 F.2d 102, 108 (C.C.P.A. 1965) (section 103 "does not contemplate degrees of skill, and, accordingly, evidence of obviousness to those not of ordinary skill is not controlling."). Alcon provides no guidance, though, as to which (Drs. Zhanel or Alfonso) or both should be ignored. Alcon clearly aims to obfuscate this issue, and its proffered definition fails to provide the Court with the requisite guidance as to the level of ordinary skill.

iv. Skill In Pharmaceutical Compounding Is The Only Skill That All Experts Agree To Be Within The Applicable Level Of Skill

Lastly, while Drs. Alfonso, Allen, and Zhanel (the only witnesses having an opinion on the issue) offer differing opinions concerning the level of ordinary skill, all have allowed for some skill in formulation. For example, Dr. Zhanel allowed that the person of ordinary skill in the art would certainly have some formulation experience, but, without explanation, would not be an expert formulator. Tr. 837:11-16.[14] Dr. Alfonso allowed that his person of ordinary skill in the art could have experience in pharmaceutical compounding. Tr. 412:7–9. Thus, it seems undisputed that the level of skill in the art includes at least some education and experience in pharmaceutical compounding. But, Dr. Allen is the only expert who has been able to quantify the minimum amount of education and skill in this area that is necessary to properly interpret and practice the '830 patent throughout its scope. Thus, his proposed definition provides the best guidance to the Court and should be adopted.

b. The Scope And Content Of The Prior Art

i. Ophthalmic Compositions Of Fluoroquinolones And Other Antibiotics Were Known In September 1998

The use of antibiotics in ophthalmic formulations was well-known in September 1998. At that time Alcon itself was selling at least three ophthalmic formulations: Ciloxan® solution (Tr. 194:6–9), Ciloxan® ointment (Tr. 203:8–11), and Tobradex® suspension (Tr. 208:16–19). Alcon was also the assignee of U.S. Patent 5,149,693, which contained an example of an ophthalmic suspension containing the antibiotic tobramycin. Furthermore, in 1998, Alcon's competitor, Allergan, was selling Ocuflox®, also a topical ophthalmic pharmaceutical

[14] That Dr. Zhanel's microbiologist's composition would be unsuitable for application to the eye (Tr. 992:11–993:22; 1004:3–14) reveals his admission that skill in formulation beyond that of a typical microbiologist is necessary to practice the subject matter of the '830 patent.

composition. Ciloxan® and Ocuflox® – both topical fluoroquinolone compositions – were state-of-the-art treatments for eye infections in September 1998. Tr. 568:12–24, 459:8–22.

ii. Moxifloxacin HCl Was Known As An Antibiotic In September 1998

Moxifloxacin HCl is also a fluoroquinolone. Tr. 430:16–19. As of September 1998, moxifloxacin HCl was known to possess antibacterial properties. Tr. 490:18–492:2. Bayer even obtained a patent covering moxifloxacin and its salts based on their antibacterial properties in 1997. See PTX 3, claim 1. Furthermore, the file history of the '942 patent also contained affidavits from a Bayer scientist that moxifloxacin HCl had a "good pharmacological profile, good activity, and *good tolerability*...." Tr. 182:9–184:24 (emphasis added) ; PTX 4, BL002-001721–35.[15]

The scientific literature available in September 1998 also reported other properties of moxifloxacin HCl. In fact, each of the properties possessed by moxifloxacin HCl and touted by Alcon's witnesses at trial (i.e., antibacterial activity, bacterial resistance profile (PTX 1124, PTX 1125, Tr. 520:24–522:25, 1045:23–1047:2, 525:21–526:13), lack of toxicity (DTX 195, p. 1399; Tr. 528:2–529:20; PTX 1098; Tr. 225:19–226:21), and ocular pharmacokinetics (Tr. 786:21–787:18)) had been disclosed in the prior art prior to the applications that lead to the '830 patent.

c. The Differences Between Claim 1 And The Prior Art

The only difference between the claimed invention and the prior art topical ophthalmic formulations (including commercial formulations marketed by Alcon) is the inclusion of moxifloxacin as the active ingredient in place of another antibiotic. This is starkly illustrated by the examples provided in the '830 patent. Each of the four examples provided in the '830 patent is nearly identical to an ophthalmic antibiotic composition known in the prior art, with the only

[15] This stands in stark contradistinction of Dr. Petersen's prior trial testimony that, in contrast with moxifloxacin HCl, the betaine was so lethal that Bayer had no further interest in it.

difference between the four examples and the prior art being the exchange of moxifloxacin for the antibiotic in the previously-known formulation. Tr. 196:22–197:18, DTX 4013 (Example 1); Tr. 209:17–211:13, DTX 4015 (Example 2); Tr. 204:15–205:16, DTX 4014 (Example 3); Tr. 213:17–214:18, DTX 4014 (Example 4).

3. As Of September, 1998 The Prior Art Predicted Topical, Ophthalmic Moxifloxacin Compositions

According to Dr. Allen, the exchange of moxifloxacin for the previously-known active antibiotics in prior art topical ophthalmic formulations was completely predictable, based on the information known in September 1998 about moxifloxacin from, for example, any of the '942 patent (Tr. 184:25–185:13), its file history (Tr. 185:6–18), the Bayer ICAAC poster (Tr. 228:7–230:5), Ciloxan® solution (Tr. 197:19–198:3), Ciloxan® ointment (Tr. 205:20–206:9), and Ocuflox® (Tr. 221:9–25). As Dr. Allen testified, a person of ordinary skill in the art in September 1998 would have reasonably expected that an ophthalmic composition in which moxifloxacin HCl was used in place of the ciprofloxacin HCl in Ciloxan® solution (as in Example 1 of the '830 patent) would have antibacterial properties and be a suitable topical ophthalmic pharmaceutical composition. Tr. 197:19–198:19. Similarly, Dr. Allen also testified that a person of ordinary skill would have found it reasonable to exchange moxifloxacin for the ciprofloxacin in Ciloxan® ointment. Tr. 205:20–206:3. According to Dr. Allen, a person of ordinary skill would have also had a reasonable expectation that a composition in which moxifloxacin HCl was exchanged for the active ofloxacin in Ocuflox® would be an antibacterial composition. Tr. 221:9–25, 222:25–223:12.

Furthermore, Dr. Allen testified that the person of ordinary skill would have been motivated by the 1997 Bayer ICAAC poster (i.e., PTX 1098) to exchange moxifloxacin for the active ciprofloxacin in Ciloxan® solution (Tr. 230:10–17) or Ciloxan® ointment (Tr. 230:18–

25), or for the active ofloxacin in Ocuflox® (Tr. 231:1–8). Dr. Allen further testified that the '942 patent would have motivated a person of ordinary skill to exchange moxifloxacin for the ciprofloxacin used in Ciloxan® solution (Tr. 200:8–16) and Ciloxan® ointment (Tr. 205:20–206:9, 207:4–8). Indeed, Dr. Allen testified that the disclosure of the '942 patent alone would have motivated a person of ordinary skill in the art to use moxifloxacin in an ophthalmic formulation. Tr. 231:24–232:16. The file history of the '942 patent would have bolstered this motivation, as it contains further information on the suitability of moxifloxacin HCl's pharmacological profile and tolerability. Tr. 185:6–24. Dr. Allen testified that, in view of this art, one skilled in the art would have reasonably expected that an ophthalmic formulation containing moxifloxacin HCl would be a pharmaceutical composition with antibacterial properties. Tr. 231:13–234:6.

Dr. Allen was the only expert to provide competent testimony as to the issue of obviousness at trial. None of Alcon's experts is actually qualified to speak from the perspective of Alcon's proffered person of ordinary skill. Dr. Alfonso does not qualify because he does not have a Ph.D in microbiology. Dr. Zhanel and Dr. Taylor both lack Medical Degrees (nor is Dr. Taylor a microbiologist). Since Drs. Alfonso, Zhanel, and Taylor admittedly are not persons having ordinary skill in the art relevant to the '830 patent, their testimony should be given little, if any, weight. Finally, Dr. Mitra did not testify to any point actually relevant to the *prima facie* case of obviousness, and his testimony should be excluded anyway, as explained above (pp 2-4). Alcon can offer no evidence to rebut Teva's *prima facie* case of obviousness.

Nevertheless, to the extent they may be heard on the issue of obviousness, each of Alcon's experts who addressed the issue all agreed that the '830 patent is not innovative. Dr. Alfonso conceded that the '830 patent did not address the issues he thought were of concern in

1998 regarding the use of fluoroquinolones to treat ophthalmic infections. Tr. 466:6–467:17. Dr. Mitra testified that there was "nothing innovative as far as the drug delivery system is concerned." Tr. 769:20–770:11. Dr. Zhanel even testified that the '830 itself patent does nothing to counter his view of the conventional wisdom,[16] i.e., that moxifloxacin would have been seen as inferior to other compounds in treating ocular infections that he felt were somehow the most important. Tr. 1025:6–15. Even Dr. Stroman, a named "inventor," actually disclaimed any inventive activity in connection with the '830 patent. Tr. 575:7–577:17.

Alcon's experts acknowledged that, in September 1998, moxifloxacin HCl was known to have antibacterial properties (Tr. 490:18–492:2; 1013:12–1015:11) and appeared to be less susceptible than ciprofloxacin to the development of resistance by at least some bacteria (Tr. 520:19–522:25, 525:21–526:13, 1045:23–1047:2). Alcon's experts also testified that, in September 1998, the literature showed moxifloxacin HCl to be sufficiently soluble (Tr. 512:17–513:21), and that it would penetrate the eye to some degree (Tr. 786:21–787:18). This shows that even all the persons of ordinary skill under Alcon's proffered definition(s) would have had, in September 1998, a reasonable expectation that a topical ophthalmic pharmaceutical composition of moxifloxacin HCl would have antibacterial properties.

4. The Prior Art Points Directly To The Use Of Moxifloxacin HCl In A Topical Ophthalmic Pharmaceutical Composition

The evidence shows that Alcon was faced with the market pressure brought about by the impending expiration of Bayer's patent on ciprofloxacin, the active ingredient in one of its key products, Ciloxan®. Not surprisingly, Alcon sent Dr. Stroman to the 1997 ICAAC to try to identify potential successors. He identified a number of potentially useful compounds, including moxifloxacin, and was eventually able to obtain "five or six" of them for testing. Tr. 572:10–17.

[16] See footnote 7.

Whether these "five or six" are reflected in the grepafloxacin, trovafloxacin, and oxazolidinone patent applications the inventors also filed on September 30, 1998 is unclear. What is clear, though, is that this case falls directly within the Supreme Court's recent admonition:

> "When there is a design need or *market pressure* to solve a problem and there are a *finite number of identified, predictable solutions*, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

KSR, 127 S. Ct. at 1742. (emphasis added)

By exchanging moxifloxacin for previously-known antibiotic compounds in prior art ophthalmic compositions without any testing of any formulation, the inventors of the '830 patent did no more than exercise common sense, with the anticipated success, later confirmed. There is no invention here. Rather, this is a "textbook case of when the asserted claims involve a combination of familiar elements according to known methods that does no more than yield predictable results." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008) (citing *KSR*, 127 S.Ct. at 1739). Claim 1 of the '830 patent plainly would have been obvious to one of ordinary skill in the art, and is therefore invalid under 35 U.S.C. § 103(a).

The *prima facie* case of obviousness is overwhelming given that Alcon's own experts and the only inventor who testified agree there is noting innovative about the '830 patent. This alone is sufficient to compel a finding of obviousness without reference to any objective indicia of nonobviousness. *See Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). Moreover, any alleged secondary considerations that Alcon may discuss will be insufficient to rebut the exceptionally strong *prima facie* case of obviousness, since any proffered secondary considerations will not be commensurate in scope with claim 1. *See In re Petersen*, 315 F.3d 1325, 1331 (Fed. Cir. 2003); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

B. Claim 1 Of The '830 Patent Is Anticipated By U.S. Patent No. 5,607,942

Assuming that claim 1 of the '830 patent is construed as Alcon contends it should be, claim 1 of the '830 patent is anticipated by Bayer's U.S. Patent No. 5,607,942. Each and every element of claim 1 of the '830 patent is disclosed in the '942 patent.

1. The Law Relating To Anticipation

Claim 1 of the '830 patent is anticipated, and therefore invalid, since every limitation in the claim is found, either explicitly or inherently, in Bayer's '942 patent. *Impax Labs., Inc. v. Aventis Pharm., Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006). The '942 patent is anticipatory even if one or more of the elements it discloses appears in a longer list without special emphasis. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005).

Where a patent claim element is directed to a range of values, that element is anticipated if a single point in that range is disclosed in a prior art reference; but, the prior art reference need not disclose the entire range in order to be anticipatory. *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 781 (Fed. Cir. 1985); *see also Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) ("[W]hen a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim."). This is consistent with the Federal Circuit's determination that a patent provides an adequate written description of a range of values, even without separately listing the values within that range, when providing the range would show a person of ordinary skill in the art that the patentee possessed the claimed invention at the time of filing. *See Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997–1001 (Fed. Cir. 2000) (holding that description of ranges was sufficient to inform one skilled in the art that inventors were in possession of specific embodiments within those ranges).

2. Every Element Of Claim 1 Of The '830 Patent Is Disclosed By The '942 Patent

The '942 patent discloses every element of claim 1 of the '830 patent. Accordingly, claim 1 is invalid as anticipated. First, the '942 patent discloses a "topical ophthalmic pharmaceutical composition." The '942 patent discloses that "[p]referred pharmaceutical formulations which may be mentioned" include, *inter alia*, solutions, suspensions, ointments, gels, and sprays. PTX 3, col. 55, ll. 1–5; Tr. 187:11–18. The '942 patent also states that the formulations mentioned can be used locally (i.e., topically) on humans, and that such local use can be accomplished through ophthalmological (i.e., ophthalmic) formulations, e.g., eye ointments or suspensions. PTX 3, col. 56, ll. 19–30; Tr. 186:17–187:10.

The '942 patent also discloses "moxifloxacin or a pharmaceutically useful hydrate or salt thereof." Claim 1 of the '942 patent identifies moxifloxacin betaine, by structure, as the preferred compound of the '942 patent, as well as unspecified salts and hydrates. PTX 3, col. 98, l. 52–col. 99, l. 2; Tr. 188:23–189:17, 243:21–244:3.

The '942 patent also discloses the third element of claim 1, "in a concentration of 0.1 to 1.0 wt %." The '942 patent states that "[t]he therapeutically active compounds should preferably be present in the abovementioned pharmaceutical formulations in a concentration of about 0.1 to 99.5, preferably about 0.5 to 95% by weight of the total mixture." PTX 3, col. 56, ll. 7–10; Tr. 189:20–190:7. As Dr. Allen testified, these ranges apply broadly to all the dosage forms listed in the '942 patent. Tr. 189:20–190:25. Moreover, he testified that a person of ordinary skill would understand that ophthalmic formulations typically have a concentration of less than 1.0 weight percent of the active ingredient testimony confirmed by the prior art Ciloxan® and Ocuflox® ophthalmic compositions, in which the concentration of active ingredients is 0.35 weight percent (Ciloxan® solution (Tr. 194:13–18)), 0.3 weight percent (Ciloxan® ointment (Tr. 202:11–203:2)), and 0.3 weight percent (Ocuflox® (Tr. 220:6–221:8)). Tr. 191:1–16. Dr. Allen testified

that a person of ordinary skill in the art would understand the '942 patent to disclose the use of moxifloxacin in a concentration within the range 0.1 to 1.0, in an ophthalmic composition. This case, thus, differs from *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991 (Fed. Cir. 2006), which lacked testimonial evidence explaining what one skilled in the art would understand from the disclosure of the prior art reference. Also, this is a case, "where the general conditions of a claim are disclosed in the prior art, [and] it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955).

The '942 patent also inherently discloses two additional ranges: 0.1 to 0.5 weight % (the difference between the low ends of the two explicitly disclosed ranges), and 95 to 99.5 weight % (the difference between the high ends of the two ranges).[17] This is further evidence that the '942 patent discloses to one skilled in the art a concentration for an ophthalmic formulation within the concentration range limitation of claim 1. Of course, the '942 patent's inherent range from 0.1 to 0.5 weight % is entirely within the range 0.1 to 1.0 weight % of the '830 patent's claim 1, and thus squarely anticipates range limitation of claim 1 of the '830 patent. *See Daiichi*, 501 F.3d at 1259, n.4.

Finally, the '942 patent discloses the last element of claim 1, "pharmaceutically acceptable vehicle therefor." The '942 patent states that the compositions disclosed therein (including ophthalmic formulations) can contain customary excipients, and then it provides copious examples of excipients. (PTX 3, col. 55, ll. 50–59; Tr. 192:15–193:5).

[17] The '942 patent does not state that either of the stated ranges is more preferred than the other, rather the '942 patent states that both ranges are preferable. (PTX 3, col. 56, ll. 7–11).

Since the '942 patent is presumed to be enabling, *Impax Labs.*, 468 F.3d at 1381–82 (Fed. Cir. 2006), and because each element of claim 1 is disclosed in the '942 patent, claim 1 is anticipated and therefore invalid under 35 U.S.C. § 102(b).

II. Claim 1 Of The '830 Patent Is Invalid For Failure To Comply With 35 U.S.C. § 112

Claim 1 is invalid for failure to comply with three requirements of 35 U.S.C. § 112, first paragraph. The '830 patent fails to provide the best mode of practicing the invention of claim 1, fails to provide an adequate written description of the invention, and fails to enable claim 1.

A. The '830 Patent Is Invalid For Failure To Provide The Best Mode Of Practicing The Invention

The '830 patent is invalid because the inventors had a best mode of making and using their invention—the use of BAY 12-8039—but they did not disclose their best mode.

1. The Law Relating To The Best Mode Requirement

The first paragraph of 35 U.S.C. § 112 requires that the specification "shall set forth the best mode contemplated by the inventor of carrying out his invention." The essence of the best mode requirement is that it "requires an inventor to disclose the best mode *contemplated by him*, as of the time he executes the application, of carrying out his invention." *Chemcast Corp. v. Arco Indus. Corp.*, 913 F.2d 923, 926 (Fed. Cir. 1990) (emphasis in original) (quotation and citations omitted). The purpose of the best mode requirement is to prevent inventors from applying for patent protection while at the same time concealing their preferred embodiments from the public. *Id.* Whether Alcon has complied with the best mode requirement is a question of fact. *Id.* at 928.

The best mode analysis has two prongs. *Chemcast*, 913 F.2d at 927. "The first is whether, at the time the inventor filed his patent application, he knew of a mode of practicing his claimed invention that he considered to be better than any other. This part of the inquiry is

wholly subjective, and resolves whether the inventor must disclose any facts in addition to those sufficient for enablement." *Id.* at 927–28; *see also Pfizer Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1364 (Fed. Cir. 2008). The second prong of the analysis compares what any Alcon inventor knew with what he disclosed—"is the disclosure adequate to enable one skilled in the art to practice the best mode or, in other words, has the inventor 'concealed' his preferred mode from the 'public'? Assessing the *adequacy* of the disclosure, as opposed to its *necessity*, is largely an objective inquiry that depends upon the scope of the claimed invention and the level of skill in the art." *Chemcast,* 913 F.2d at 928 (emphasis in original).

"Best mode requires inventors 'to disclose aspects of making or using the claimed invention [when] the undisclosed matter materially affect[s] the properties of the claimed invention.'" *Pfizer*, 518 F.3d at 1364 (quoting *Bayer AG v. Schein Pharm., Inc.*, 301 F.3d 1306, 1319 (Fed. Cir. 2002)). "[W]here the inventor has failed to disclose the only mode he ever contemplated of carrying out his invention, the best mode requirement is violated." *Chemcast,* 913 F.2d at 930 (citations omitted).

The question of whether the undisclosed best mode is somehow enabled is irrelevant to the best mode inquiry. *Bayer AG*, 301 F.3d at 1314 ("Because of the subjective nature of the best mode inquiry, the best mode disclosure requirement—unlike enablement—cannot be met by mute reference to the knowledge of one of skill in the art. The reason is pragmatic. It is unreasonable if not impossible to require the ordinary artisan to peer into the inventor's mind to discover his or her idiosyncratic preferences as of the filing date."). Rather, actual disclosure of Alcon's inventors best mode is required, whether it is otherwise enabled or not. *See id.*

2. Dr. Stroman Knew Of Only One Mode And Did Not Disclose It

There is no dispute that the only form of moxifloxacin that Dr. Stroman knew about in September 1998 was BAY 12-8039 (moxifloxacin HCl), based on his attendance at the 1997

ICAAC conference and Bayer's presentation. Tr. 641:16–24. While Dr. Stroman may not have known the chemical structure of BAY 12-8039 until well after September 1998, he conceded that he knew how to identify the compound he was interested in by its name: BAY 12-8039. Tr. 579:3–11; see also PTX 1065.

Here, as in *Chemcast*, Dr. Stroman knew but one mode of practicing his "invention," and this single mode is *ipso facto* his best mode. There is no question that BAY 12-8039 is not disclosed in the '830 patent, either by name, synonym, structure, or otherwise. Dr. Stroman unquestionably knew enough about the compound to identify it in his February 1998 request to Bayer (PTX 1065), so 35 U.S.C. § 112 required him to disclose the compound in his patent. Even if Dr. Stroman "did not know the composition or method of manufacture of [BAY 12-8039], he was required, at a minimum, to provide supplier/trade name information in order to satisfy the best mode requirement." *U.S. Gypsum Co. v. Nat'l Gypsum Co.*, 74 F.3d 1209, 1214 (Fed. Cir. 1996). By failing to disclose his only contemplated mode of practicing the invention, Dr. Stroman violated the best mode requirement.

While the '830 patent refers to "moxifloxacin," there is no evidence that the inventors somehow meant moxifloxacin HCl as opposed to moxifloxacin betaine. Furthermore, there is no evidence that any of the inventors had any knowledge as of the effective filing date of the '830 patent regarding moxifloxacin betaine, or the relative properties of moxifloxacin HCl and moxifloxacin betaine. Bluntly, they could not have, since Dr. Stroman did not even know then that moxifloxacin betaine existed, and therefore could not have known about its properties. The first time that Alcon ever requested the betaine was in December 2007, and only because of issues raised during this litigation. Tr. 678:7–679:21.

Any argument that moxifloxacin betaine and moxifloxacin HCl are the same is contradicted even by Alcon's own experts. Dr. Taylor, Alcon's organic medicinal chemistry expert, confirmed that the two are different compounds in their own right and that a solution made with BAY 12-8039 would have a different pH than a solution made with the betaine. Tr. 95:6–13. In turn, Dr. Alfonso testified that the pH of an ophthalmic solution has an effect on the ophthalmic tolerability of that solution, as a relatively low pH can sting the eyes. Tr. 461:8–18. Moreover, Dr. Taylor also testified that hydrochloride salts are "known and are prepared not only because of their convenience in preparation, their storage capabilities, their stabilities and the like but also *for their solubilities*." Tr. 143:15–22 (emphasis added). This testimony reveals that the salt form can have a material effect on the way a formulation is made and used. Moreover, prior testimony received in this Court was that moxifloxacin betaine was too lethal for Bayer to be interested in development of moxifloxacin betaine (Trial Transcript, *Bayer AG et al. v. Dr. Reddy's Labs., Ltd.*, C.A. 04-179-SLR, pp. 313:12–314:1 (Aug. 8, 2006)), in stark contrast with Bayer's manifest interest in and successful development of moxifloxacin HCl as a commercial product (Avelox®).

Because the inventors of the '830 patent were aware of only one mode (the use of moxifloxacin HCl (i.e., BAY 12-8039)) of making their "invention," yet did not disclose that mode in the '830 patent, they failed to "set forth the best mode contemplated by the inventor[s] of carrying out [their] invention." Accordingly, the '830 patent is invalid under 35 U.S.C. § 112.

B. Claim 1 Of The '830 Patent Is Invalid For Failure To Include An Element That The Specification States Is Essential

35 U.S.C. § 112 requires that the "specification shall contain a written description of the invention...." *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The "written description" requirement is broader than simply a description of how to "make and use"

the invention; rather, the '830 patent must convey to those skilled in the art that, as of the filing date, the inventor was in possession of the claimed invention. *Id.* at 1563–64. Specifically, the patent's "description must clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Id.* at 1563 (quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)).

Here, the '830 patent fails to comply with the written description requirement by claiming the invention more broadly than the invention is described in the patent's specification. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998). The written description of the invention requires the ophthalmic compositions to include a preservative. PTX 5, col. 5. l. 66–col. 6, l. 1. Claim 1 is broader than the described invention, though, because the claim 1 composition does not require a preservative. PTX 5, col. 7, ll. 29–32. As such, claim 1 is broader than the supporting disclosure and is invalid. *Gentry Gallery, 134 F.3d* at 1480.

The specification of the '830 patent presents a list of suitable preservatives (PTX 5, col. 5, l. 66–col. 6, l. 9), not one of which is identified as synonymous with the active agent. The specification also provides a catch-all statement, that "other agents known to those skilled in the art" can also act as preservatives in the compositions of the '830 patent. PTX 5, col. 6, l. 5. Moxifloxacin is not mentioned, and there is no evidence that moxifloxacin was known in the art to be a preservative for ophthalmic compositions in September 1998.[18] Accordingly, reference to a "preservative" shows that the patent requires a preservative separate from the active ingredient.

[18] Indeed, if moxifloxacin were known to those skilled in the art as a preservative in ophthalmic formulations, then claim 1 of the '830 patent is necessarily anticipated by that very prior art, as topical ophthalmic moxifloxacin would, *ipso facto*, have to have been known previously.

Example 3 of the '830 patent does not support the broader claim. There is no evidence that Alcon ever made or tested the formulation of Example 3, and there is no evidence whether that formulation is self-preserving due to the presence of moxifloxacin. In any event, this wholly prophetic Example, obviously cobbled wholesale from some other product, should not trump the inventors' affirmative statement that a preservative is "required" to practice their invention, such as it is. In this respect, the '830 patent need not be construed in such a manner that it includes all examples listed in the patent's specification. *Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1138 (Fed. Cir. 2007) ("we have previously interpreted claims to exclude embodiments where those embodiments are inconsistent with unambiguous language in the patent's specification or prosecution history.") (citations omitted).

Alcon overclaimed here by omitting an element that the specification affirmatively states is *required*. Accordingly, the '830 patent fails to convey to those skilled in the art that, as of the filing date, the inventors were in possession of what is recited in claim 1. Accordingly, in addition to violating the "written description" prong of Section 112, claim 1 also violates the "enablement" prong as well. *In re Mayhew*, 527 F.2d 1229, 1233 (C.C.P.A. 1976). Claim 1 is, therefore, invalid under 35 U.S.C. § 112.

C. If The Court Accepts Alcon's Person Of Ordinary Skill In The Art, Then The '830 Patent Is Invalid For Lack Of Enablement

As alluded to above, the '830 patent does not enable "one" skilled in the art, as defined by Alcon, to make and use the full scope of the invention claimed in claim 1 without undue experimentation.

1. The Law Relating To Enablement

The specification must enable one of ordinary skill in the art to practice the full scope of the invention; this requirement is "part of the *quid pro quo* of the patent bargain." *Liebel-*

Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371, 1380 (Fed. Cir. 2007) (citation omitted). This requirement ensures that the public's knowledge is enriched by the teachings of the patent to a degree at least as broad as the scope of the claims. *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008) (quoting *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195–96 (Fed. Cir. 1999)).

Further, enablement "requires that the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Factors to be considered in determining whether a disclosure would require undue experimentation include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.*

Also, where a claim is broad enough to cover multiple categories of embodiments, the patent must enable each category. *Sitrick* 516 F.3d at 1000. ("Because the asserted claims are broad enough to cover both movies and video games, the patent must enable both embodiments."). Thus, because claim 1 of the '830 patent covers multiple types of topical ophthalmic pharmaceutical compositions (e.g., solutions, ointments, gels, etc.) (PTX 5, col. 2, ll. 47–51; Tr. 186:17–188:6), its specification must enable each. Furthermore, such compositions must be sterile, non-irritating, convenient to administer, stable, and have a non-toxic vehicle. Tr. 275:18–277:3.

2. The '830 Patent Does Not Enable The Person Of Ordinary Skill In The Art Proffered By Alcon To Practice The Invention Of Claim 1, Violating § 112

If Alcon's definition is accepted, the '830 patent's disclosure fails to enable the claimed invention. The definition of the "person" of ordinary skill proffered by Alcon's experts must

have the skills and experience of a microbiologist "and/or" an ophthalmologist. Tr. 406:1–407:2, 444:14–445:3, 988:18–989:5. By offering its ambiguous "definition," Alcon fails to provide the Court with any guidance as to the relative level of skill in the art (*Wands* factor no. 6). Alcon's purported persons of ordinary skill lack sufficient knowledge in pharmaceutical compounding to make the full scope of topical ophthalmic compositions containing moxifloxacin claimed in claim 1 without undue experimentation.

The disclosure of the '830 patent also does not provide sufficient information to explain *how* such a composition can be made, as no process steps for making formulations are provided (*Wands* factor no. 2). PTX 5; Tr. 447:6–22. What is more, the '830 patent's four Examples are not "working" examples as they were described in provisional applications before anyone at Alcon had received moxifloxacin from Bayer (*Wands* factor no. 3). Tr. 648:11–649:11. Indeed, Dr. Stroman testified that he did not know if anyone at Alcon had *ever* made the formulations described in the Examples of the '830 patent prior to this litigation. Tr. 662:21–663:4, 664:14–666:5. Furthermore, the '830 patent refers, in the context of discussing potential formulation ingredients, to "other agents known to those skilled in the art" (*Wands* factor no. 5). PTX 5, col. 5, l. 66–col. 6, l. 29. A formulator would know of such agents, but it does not follow from Drs. Alfonso's or Zhanel's testimony that an ophthalmologist or microbiologist would, or even that they are likely to.

Dr. Alfonso agreed that the '830 patent does not provide instructions as to any process to be used to make any formulations within the scope of claim 1 (*Wands* factor no. 2). Tr. 447:6–447:22. When further pressed on cross-examination for details of making the formulations of the examples, he conceded that much more information than that provided in the '830 patent was needed in order to make these formulations. For example, Dr. Alfonso testified that water would

be the last ingredient he would add in making the formulation of Example 1. Tr. 448:1–449:2. This is in direct contrast to the testimony of Dr. Allen (to whom Alcon's experts have deferred as an expert in formulation) who testified that the first formulation step is to *start* with water and then add other ingredients. Tr. 199:15–200:4.[19] With respect to Example 2, a suspension, Dr. Alfonso first testified again that water would be the last ingredient added (simplistically, because it is the last ingredient listed in Example 2) before backtracking because he recognized that it would be improper to add water after adding sulfuric acid or sodium hydroxide to adjust pH. Tr. 449:18–450:24. Dr. Alfonso also speculated that he "probably" could make Example 3, an ointment, although he was quite unsure as to how the mixing of the ingredients should occur. Tr. 452:5–23. Finally, Dr. Alfonso testimony reveals that he was unfamiliar with the process steps involved in making the composition of Example 4. Tr. 453:4–455:7. Dr. Alfonso's testimony reveals that undue experimentation would be necessary for his persons of ordinary skill in the art to make formulations of claim 1 of the '830 patent (*Wands* factor no. 1). In fact, he has never formulated any of these Examples, and in his practice, he relies on the skill of others in his laboratory to actually make the formulations he uses. Tr. 454:17-25.

Next, Dr. Zhanel deferred to Dr. Allen on matters of pharmaceutical formulation, and claimed not to have expertise in pharmaceutical compounding. Tr. 1002:18–1003:16, 1077:18–1078:3. Dr. Zhanel did say that he and his microbiology students could prepare certain microbiological formulations containing moxifloxacin, but, when pressed on cross-examination, revealed that such formulations are not suitable for administration to patients (and thus are not

[19] Dr. Alfonso's proposed protocol is also not consistent with the manner in which Ms. Alford, one of Alcon's fact witnesses, actually prepared a solution with the ingredients of Example 1. Tr. 681:16–684:5.

"pharmaceutical" compositions[20]). Tellingly, he conceded he would not allow those formulations into his eye. Tr. 992:11–993:22, 1004:3–1004:14. This concession reveals that formulations made by Alcon's various persons of ordinary skill in the art would not be pharmaceutical formulations within the scope of claim 1 (*Wands* factor no. 7).

As stated above, Dr. Taylor disclaimed any expertise in formulation, and Dr. Mitra provided no testimony as to the level of ordinary skill in the art. Ms. Alford, who testified on behalf of Alcon, stated that she made a "solution" supposedly in accordance with Example 1 of the '830 patent. On cross-examination, though, she revealed that she did not know whether this was a "pharmaceutical" formulation, as she did not test it for osmolality (mistakenly called "modality" in the transcript), tonicity, sterility, or even activity. Tr. 690:4–690:25. Ms. Alford did not make an ointment or suspension containing moxifloxacin, nor any other type of composition commensurate with the scope of claim 1. There is no evidence as to Ms. Alford's level of skill, although the fact that she has not been awarded either a Ph.D. or M.D. would appear to preclude her from being a person of ordinary skill under any of Alcon's experts' definitions.

If Alcon's witnesses are unable to make a topical ophthalmic pharmaceutical composition according to the '830 patent, then they also should not be heard to offer an opinion as to how a person of ordinary skill in the art would make any such composition. What is more, their opinions regarding who the person of ordinary skill in the art is are not based on any relevant work or experience. Such opinions offered by Alcon's experts who are not skilled in the relevant art and which are conclusory and unsupported by actual information are insufficient to show that

[20] Dr. Zhanel opined that the phrase "topical ophthalmic pharmaceutical composition" indicates use in humans (*Wands* factor no. 4). Tr. 1117:21–1118:2.

claim 1 of the '830 patent is enabled. *See Sitrick*, 516 F.3d at 1001 (stating that such opinions fail even to raise an issue of fact sufficient to defeat a motion for summary judgment). Thus, Alcon's experts' testimony on this point is simply not credible, and the Court should not accept it.

Alcon's expert's equivocation as to whether Alcon's persons of ordinary skill in the art could, based on the disclosure of the '830 patent, make ophthalmic formulations according to claim 1 of the '830 patent is not evidence of enablement. *Id.* Even if one of Alcon's witnesses were able to make a pharmaceutical *solution* in accordance with claim 1 of the '830 patent (of which there is no evidence), there was clearly no testimony that supports the conclusion that the person(s) of ordinary skill in the art as defined by Alcon's experts would be able to formulate a proper gel, suspension, ointment or any other type of composition embraced by the breadth of claim 1 of the '830 patent (*Wands* factor no. 8). Section 112, however, requires that *all* types of embodiments covered by the claim be enabled. *Id.* at 1000. That would clearly not be the case for the '830 patent if any of Alcon's experts' definitions were accepted.

CONCLUSION

For the foregoing reasons, if the Court construes "moxifloxacin" as Alcon alleges, then claim 1 is invalid under 35 U.S.C. § 103(a) as obvious and under 35 U.S.C. § 102(b) as anticipated. Regardless of the Court's claim construction, though, claim 1 of the '830 patent is invalid under 35 U.S.C. § 112.

May 22, 2008

THE BAYARD FIRM

/s/ Richard D. Kirk (rk0922)
222 Delaware Avenue, Suite 900
P.O. Box 25130
Wilmington, DE 19899-5130
(302) 655-5000
Counsel for Defendant,
TEVA PHARMACEUTICALS USA, INC.

OF COUNSEL:

Bruce M. Gagala
M. Daniel Hefner
Douglas A. Robinson
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
Chicago, Illinois 60601

CERTIFICATE OF SERVICE

The undersigned counsel further certifies that, on May 22, 2008, copies of the foregoing document were sent to the following in the manner shown:

BY EMAIL AND BY HAND

Frederick L. Cottrell III, Esquire
Jeffrey L. Moyer, Esquire
Anne Shea Gaza, Esquire
Richards, Layton & Finger, P.A.
One Rodney Square
920 North King Street
Wilmington, Delaware 19801

BY EMAIL AND
BY OVERNIGHT COURIER

Bruce R. Genderson, Esquire
Adam L. Perlman, Esquire
Dov P. Grossman, Esquire
David I. Berl, Esquire
Aaron P. Maurer, Esquire
Williams and Connolly
725 Twelfth Street, N.W.
Washington, D.C. 20005

/s/ Richard D. Kirk (rk0922)
Richard D. Kirk